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Original article

Mean platelet volume and its relation to insulin resistance in non-diabetic patients with slow coronary flow

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KEYWORDS
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Summary
Background: Increased mean platelet volume is a central process in the pathophysiology of coronary heart disease. Insulin resistance contributes to increased platelet activation.
Aim: To assess the mean platelet volume and its possible relationship with insulin resistance in non-diabetic patients with slow coronary flow.
Methods and subjects: The study included 60 patients with slow coronary flow and 20 subjects (controls) with normal coronary arteries. Slow coronary flow patients were divided into 2 groups, insulin resistant (32 patients) and insulin sensitive (28 patients) according to the homeostasis model assessment of insulin resistance index (HOMA-IR).
Results: Patients with slow coronary flow had significantly higher mean platelet volume values (7.9 ± 0.47 vs. 7.1 ± 0.5, $p < 0.01$), insulin level (10.8 ± 3.2 vs. 8.2 ± 1.4, $p < 0.01$), and HOMA-IR scores (2.72 ± 0.85 vs. 1.84 ± 0.19, $p < 0.01$). These parameters were significantly higher in insulin-resistant patients than in insulin-sensitive ones. The mean platelet volume was correlated with HOMA-IR ($r = 0.52$, $p < 0.01$) and insulin level ($r = 0.58$, $p < 0.01$). In multivariate analysis, mean platelet volume and HOMA-IR were independent predictors of mean TIMI frame count {($B \pm SE = 0.562 \pm 2.95$, $p < 0.01$) and ($B \pm SE = 0.538 \pm 2.46$, $p < 0.01$), respectively}.
Conclusion: Patients with slow coronary flow have increased mean platelet volume which was associated with insulin resistance in non-diabetic slow coronary flow patients. TIMI frame counts correlated with mean platelet volume and increased insulin resistance. Thus, insulin resistance and platelet activity may have a role in the pathogenesis of slow coronary flow. Also, they may have a possible benefit as follow-up markers in non-diabetic patients with slow coronary flow.

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Introduction

Coronary slow flow (CSF) is characterized by late opacification of the epicardial coronary arteries without occlusive disease [1]. The exact pathophysiologic mechanisms of CSF phenomenon remain uncertain. Small vessel dysfunction has been implicated in the pathogenesis of CSF phenomenon since its first description [2,3]. It has been reported that coronary endothelial dysfunction plays an important pathogenetic role in patients with CSF [4]. In addition, platelet function disorders have also been suggested to be involved in the development of CSF [5]. Mean platelet volume (MPV) is one of the platelet function indices that reflects the platelet production rate and stimulation [6]. It has been reported that elevated values of MPV are associated with various cardiovascular diseases [7]. Elevated values of MPV are considered as a marker of increased thromboembolic risk in mitral stenosis patients [8].

In CSF syndrome, it has been suggested that an insulin-resistant state may lead to the development of coronary microvascular dysfunction before the development of overt diabetes mellitus [9]. Insulin resistance is associated with a functional change in platelets that promotes thrombosis. Decreased vascular endothelial production of prostacyclin and nitric oxide in patients with insulin resistance promotes increased activation of platelets [10].

To the best of our knowledge, no study has investigated specifically the direct relationship between insulin resistance and MPV in non-diabetic CSF patients to advise a treatment strategy for these patients. Accordingly, the aim of our study was to evaluate the relationship between MPV and insulin resistance in non-diabetic CSF patients.

Patients and methods

Sixty patients with CSF as evidenced by coronary angiographic results and 20 control subjects with normal coronary arteries were included. Patients with CSF were subdivided into two groups depending on the presence of insulin resistance, an insulin-resistant group (32 patients) and an insulin-sensitive group (28 patients).

Exclusion criteria were patients with known coronary artery disease, coronary plaque on coronary angiography, peripheral artery disease, valvular heart disease, left ventricular ejection fraction less than 50%, thrombocytopenia, renal and hepatic impairment, chronic inflammatory disease, malignancy, thyroid hormonal dysfunction, pregnancy, septicemia, cerebrovascular accident, uncontrolled hypertension, and treatment for hyperlipidemia. To avoid the influence of disturbances in insulin secretion, all subjects with diabetes mellitus (fasting glucose >125 mg/dl or glucose in 120 min of oral glucose tolerance test >200 mg/dl), anti-inflammatory drugs within the previous 3 months, or any drugs known to affect carbohydrate and lipid metabolism were excluded from this study. The study was approved by the basal ethical committee of our hospital and all patients gave written consent.

Coronary arteriography was performed by a femoral approach using the standard Judkins technique for subjects who suffered from angina and angina-like symptoms (shortness of breath, palpitation, etc.) and their symptoms could not be adequately clarified with non-invasive tests.

Slow coronary flow and thrombolysis in myocardial infarction frame count

To measure coronary blood flow, the time elapsed from the appearance of the contrast agent until it reached the distal end of either left anterior descending (LAD) artery, circumflex artery, or the right coronary artery in terms of cine frame count was considered to be the thrombolysis in myocardial infarction (TIMI) frame count. Distal end was defined as distal bifurcation for LAD and circumflex artery and first branch of posterolateral artery for right coronary artery. The final count was subtracted from the initial count and the exact TIMI frame count was calculated for the given artery. However, it was divided by 1.7 when LAD artery was the case for adjusted correction. TIMI frame counting was done by two separate cardiologists. The cutoff values were defined according to TIMI frame count method by Gibson et al. [11], 36.2 ± 2.6 frames for LAD, 22.2 ± 4.1 frames for circumflex, and 20.4 ± 3.0 frames for right coronary artery. The corrected cutoff value for LAD coronary artery was 21.3 ± 1.5 frames. Any frame count above these thresholds was considered CSF.

Blood samples and analysis

Blood samples were collected from the patients after a 12 h overnight fasting. All routine biochemical tests were carried out on an autoanalyzer. MPV was analyzed using blood samples with K3 EDTA that were analyzed after 1 h of venipuncture to allow stabilization of platelet shape and to prevent EDTA-induced swelling. The estimate of insulin resistance by homeostasis model of assessment (HOMA-IR) derives an estimate of insulin sensitivity from the mathematical modeling of fasting glucose and insulin concentrations [10]. In comparison with the euglycemic clamp, the HOMA-IR model is an easy, practical, and inexpensive method for assessing IR. We applied the HOMA-IR in non-diabetic participants using the following formula [12]; fasting insulin level (μU/mL) $\times$ fasting glucose (mg/dL)/405. Subjects whose values exceeded the 75th percentile (i.e. 2.0) were considered to have insulin resistance (HOMA-IR index) [13].

Statistical analysis

Continuous variables were expressed as mean $\pm$ SD and categorical variables are expressed as percentages. Comparison of variables between the two groups was performed using the χ^2 test and Student's t-test. The correlation between mean TIMI frame count and MPV, HOMA-IR, and other measurements was assessed by the Pearson correlation analysis. Multivariate linear regression analysis was used to find the significant independent predictors of mean TIMI frame count.

Results

Demographic and clinical characteristics of the study population are presented in Table 1. No significant difference

Table 1 Demographic and clinical characteristics of the study population.

	Group I	Group II	*p*-Value
Age (years)	58.41 ± 6.53	56.84 ± 7.40	0.43
Pulse (beat/min)	71.70 ± 8.21	72.02 ± 6.81	0.71
Systolic blood pressure (mmHg)	133.74 ± 16.62	132.83 ± 14.61	0.25
Diastolic blood pressure (mmHg)	76.76 ± 12.63	75.80 ± 11.36	0.54
Fasting glucose (mg/dL)	95.60 ± 11.82	90.22 ± 10.72	0.08
Hemoglobin A1c, (%)	5.32 ± 0.41	5.30 ± 0.36	0.22
HOMA-IR index	2.70 ± 0.85	1.84 ± 0.23	<0.01
Insulin level (μU/mL)	10.81 ± 3.27	8.21 ± 1.44	<0.05
Mean platelet volume (fl)	7.90 ± 0.47	7.17 ± 0.52	<0.01
Hypertension	18 (30.00%)	7 (35.00%)	0.72
Triglycerides (mg/dL)	130.33 ± 43.94	128.11 ± 40.43	0.64
Total cholesterol (mg/dL)	179.85 ± 28.62	181.31 ± 19.80	0.56
HDL (mg/dL)	40.90 ± 6.53	41.45 ± 6.92	0.73
LDL (mg/dL)	91.44 ± 31.72	90.70 ± 29.81	0.81
Medications			
ACE inhibitors	12 (20.00%)	5 (25.00%)	0.76
Beta-blockers	16 (26.66%)	6 (30.00%)	0.79
Calcium-channel blockers	17 (28.33%)	5 (25.00%)	0.82
Statin	16 (26.66%)	6 (30.00%)	0.79

HOMA-IR, insulin resistance by homeostasis model of assessment; HDL, high-density lipoprotein; LDL, low-density lipoprotein; ACE, angiotensin-converting enzyme.

was found between patients with CSF and controls with respect to age, sex, body mass index (BMI), total cholesterol, low-density lipoprotein cholesterol (LDL-C), high-density lipoprotein cholesterol (HDL-C), and HbA1C (all $p > 0.05$). Patients with CSF had higher MPV (fl), insulin levels (μU/mL), and HOMA-IR index compared with control participants ($p < 0.01$).

The mean TIMI frame count was found to be significantly higher in the CSF group compared with the control group (52.6 ± 10.3 vs. 18.6 ± 3.3, $p < 0.001$). Mean

Table 2 The clinical and laboratory characteristics of the insulin-resistant and insulin-sensitive patients with coronary slow flow.

	Insulin resistant (32)	Insulin sensitive (28)	*p*-Value
Age	57.52 ± 5.23	54.84 ± 6.81	0.08
Systolic BP (mmHg)	140.42 ± 21.31	136.22 ± 4.92	0.28
Diastolic BP (mmHg)	81.42 ± 10.13	78.11 ± 12.30	0.26
Hemoglobin (g/dl)	14.12 ± 1.58	14.20 ± 1.41	0.63
Fasting blood glucose (mg/dL)	98.33 ± 14.91	90.24 ± 13.39	0.15
Body mass index (kg/m^2)	30.14 ± 2.53	24.50 ± 2.82	<0.05
Insulin level (uU/mL)	11.81 ± 3.13	8.23 ± 1.57	<0.01
Platelet count (×10^3/μL)	249.22 ± 74.25	228.31 ± 61.45	0.21
Platelet volume (fl)	8.25 ± 0.48	7.55 ± 0.25	<0.01
WBCs (×10^3/μL)	7.50 ± 2.34	7.36 ± 2.73	0.75
Triglycerides (mg/dL)	131.10 ± 47.52	125.80 ± 42.79	0.66
Total cholesterol (mg/dL)	188.03 ± 28.53	176.89 ± 19.70	0.08
LDL (mg/dL)	96.32 ± 26.22	94.71 ± 27.12	0.82
HDL (mg/dL)	40.80 ± 6.24	43.70 ± 5.83	0.06
Drugs: beta-blockers	8 (25.00%)	8 (28.57%)	0.75
Calcium-channel blockers	10 (31.25%)	7 (25.00%)	0.64
Statins	8 (25.00%)	8 (28.57%)	0.75
ACE inhibitors	4 (12.50%)	8 (28.57%)	0.12
Aspirin	7 (21.87%)	6 (21.42%)	0.96

BP, blood pressure; WBC, white blood cell; LDL, low-density lipoprotein; HDL, high-density lipoprotein; ACE, angiotensin-converting enzyme.

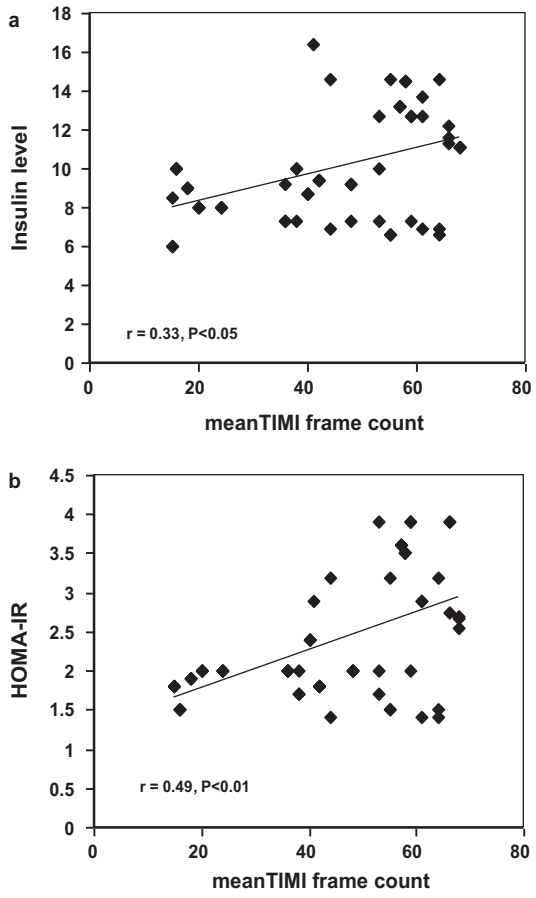

Figure 1 (a) Correlation between mean thrombolysis in myocardial infarction (TIMI) frame count and insulin level. (b) Correlation between mean TIMI frame count and insulin resistance by homeostasis model of assessment (HOMA-IR).

TIMI frame count was significantly correlated with MPV (fl), fasting plasma insulin levels, and HOMA-IR index ($r = 0.6$, $p < 0.01$, $r = 0.43$, $p < 0.01$, $r = 0.49$, $p < 0.01$, respectively) (Fig. 1a,b and 2). At multiple regression analysis mean TIMI frame count correlated independently with MPV ($B \pm SE = 0.562 \pm 2.95$, $t = 5.66$, $p < 0.01$) and HOMA-IR index ($B \pm SE = 0.538 \pm 2.46$, $t = 4.37$, $p < 0.01$).

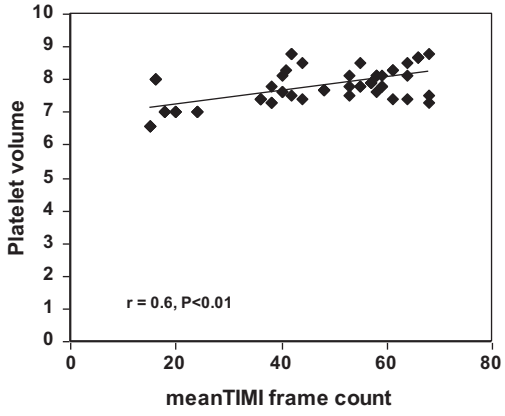

Figure 2 Correlation between mean thrombolysis in myocardial infarction (TIMI) frame count and mean platelet volume.

Table 3 Correlation of mean platelet volume (fl) with other parameters.

	r	*p*-Value
HOMA-IR	0.52	<0.01
Insulin level	0.58	<0.01
Total cholesterol	0.14	>0.05
Triglycerides	0.15	>0.05
Fasting blood glucose	0.06	>0.05
Systolic BP	0.19	>0.05
Diastolic BP	0.17	>0.05
LVMI	0.37	<0.05

HOMA-IR, insulin resistance by homeostasis model of assessment; BP, blood pressure; LVMI, left ventricular mass index.

The clinical and laboratory characteristics of the insulin-resistant and insulin-sensitive patients with CSF are presented in Table 2. There were no statistically significant differences between the two groups with respect to age, levels of glucose (mg/dl), WBCs, total cholesterol, triglyceride, LDL-C, or HDL-C. MPV (fl), insulin (μU/mL) and body mass index were significantly higher in insulin-resistant CSF patients than in insulin-sensitive CSF patients ($p < 0.01$ for all). The MPV was correlated with HOMA-IR index ($r = 0.52$, $p < 0.01$) and insulin level ($r = 0.58$, $p < 0.01$) (Table 3).

Discussion

The present study investigated the relationship between MPV and insulin resistance in non-diabetic patients with CSF. The study found that MPV and insulin resistance are higher in CSF patients. MPV, an indicator of platelet activation, was higher in insulin-resistant CSF patients than in insulin-sensitive CSF patients.

CSF phenomenon is an important clinical entity because it may be the cause of angina at rest or during exercise, acute myocardial infarction, and hypotension [14—16].

However, only a limited number of studies have focused on the etiology of this unique angiographic phenomenon. It has been reported that coronary endothelial dysfunction plays an important pathogenetic role in patients with CSF [4]. Moreover, myocardial biopsy studies have also revealed the presence of coronary microvascular disease in patients exhibiting CSF [17]. Platelet function disorders have also been suggested to be involved in the development of CSF as the platelet aggregability increased in patients with CSF compared with controls [5] suggesting an altered platelet reactivity and aggregation which may require effective antiplatelet therapy in CSF patients. However, the association of MPV with insulin resistance, which has been accepted as one of the risk factors for CAD, has gained little attention.

Platelets play an important role in the integrity of normal homeostasis, and MPV is the indicator for its function and activity [18]. The large platelets having dense granules are more active biochemically, functionally, and metabolically, have higher thromboxane A2 levels, express more glycoprotein Ib and IIb/IIIa receptors, and could be a risk factor for developing coronary thrombosis [18,19].

The present study showed that MPV increased in CSF patients compared with the control group. In addition, a positive correlation was found between TIMI frame count and MPV. In previous reports, there are different methods that were used for the analyses of platelet activation; optical aggregometry, platelet function analyzer (PFA-100), platelet reactivity test, platelet aggregate ratio, flow cytometry, and thromboxane B_2 generation [20]. All tests have limitations in their use due to complex pre-analytic factors, reduced specificity, and poor reproducibility. However, MPV is a simple marker, not requiring an advanced or expensive technology [20].

The present study showed that insulin resistance increased in CSF patients compared to control with significant positive correlation with TIMI frame count. The study used the HOMA-IR to estimate insulin sensitivity.

Ozcan et al. found that in patients with CSF, TIMI frame counts and high sensitivity C-reactive protein are correlated with increased insulin resistance (HOMA-IR) and thus, it can be suggested that insulin resistance and inflammation may, in part, have a role in the pathogenesis of CSF [21]. Also, Binak et al. [9] investigated impaired glucose tolerance in patients with CSF and suggested that impaired glucose tolerance may be an independent etiological factor for CSF phenomenon. On the basis of these findings and literature data, it can be suggested that an insulin-resistant state may, in part, play a role in the pathogenesis of CSF.

Recently, Varol et al. showed that MPV was significantly elevated in insulin-resistant, non-obese, non-diabetic CAD patients when compared to insulin-sensitive, non-obese, non-diabetic CAD patients [22].

The present study investigated the direct relationship between insulin resistance and MPV in patients with CSF. MPV was higher in insulin-resistant patients with CSF than in insulin-sensitive CSF patients. In another study, Yazici et al. found that MPV values were significantly higher in patients with insulin resistance than in patients without insulin resistance in prehypertension subjects [23]. Insulin resistance is associated with a functional change in platelets that promotes thrombosis [24]. In conditions of insulin resistance, a reduction in platelet sensitivity to the anti-aggregating effects of insulin has been reported [5,25,26]. Decreased vascular endothelial production of prostacyclin and nitric oxide in patients with insulin resistance promotes increased activation of platelets [10]. Another mechanism is the increased platelet reactivity due to the direct effect of hyperglycemia via osmotic effects on platelets [27]. Insulin resistance, diabetes mellitus, and other risk factors associated with endothelial dysfunction might trigger a series of cytokine production which in turn may stimulate the production of large platelets in the bone marrow [28].

The present study was limited by the small sample size. Also, the effect of the volume, rate, and pressure of the contrast injection on the measurement of TIMI frame count should be considered as a limitation. Data evaluating inflammatory parameters such as high-sensitivity C-reactive protein and evaluating endothelial function such as flow-mediated vasodilatation were not performed. Further research with a large sample size to evaluate high-sensitivity C-reactive protein and endothelial function is recommended.

Conclusion

MPV and insulin resistance increased in CSF non-diabetic patients. In the light of these findings, it can be suggested that they may, in part, have a role in the pathogenesis of CSF. There is a close relationship between insulin resistance and MPV. We can establish the clinical significance of increased MPV in CSF. MPV and HOMA-IR may have possible benefit as follow-up markers during the management of CSF patients.

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